



IST-GU-102 Phase I/II study of nivolumab and axitinib in patients with advanced renal cell carcinoma

Supported by (Bristol-Myers Squibb)

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## Schema

### **Population**

**Phase I (3+3 design)-** 6-12 patients exposed to at least 1 prior TKI therapy

**Phase II-** 2 parallel arms with 43 patients each.

Arm 1: 43 treatment naïve patients

Arm 2: 43 patients exposed to at least 1 prior TKI therapy



### **Treatment (28 days per cycle):**

**Phase I-** Axitinib given initially at a dose of 3 mg PO BID for 1 week starting on day -7 (+3 days) in the Lead-In phase, followed by Axitinib 3 mg PO BID + Nivolumab given as 30 min IV at 480 mg every 4 weeks for up to 2 years or until disease progression. Dose escalation/de-escalation of Axitinib based on toxicity assessment by pre-specified DLT rules, which will determine Phase II dosing



### **Phase I DLT Assessment**

Cycle 1 and 2

### **Phase II Disease Assessment**

Radiological tumor assessments conducted at baseline, after 8 weeks of combination and every 3 cycles thereafter



### **Continue treatment until:**

- Disease progression
- Unacceptable toxicity
- Patient withdraw of consent
- Patient lost to follow up
- Study is terminated by the Sponsor
- Completion of therapy after 24 months



### **Follow up**

- Every 3 months for the first 2 years, then every 6 months for 2 years, and then annually for survival.
- Subjects who discontinue treatment for reasons other than disease progression should continue to have radiographic assessments of disease at least every 12 weeks until documented disease progression.

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## **1.0 Introduction**

### **1.1. Study Disease**

Advanced renal cell carcinoma (RCC) is an incurable disease accounting for more than 10,000 new cases of metastatic disease diagnosed annually in the United States and nearly 14,000 deaths.[1] Prior to 2005, treatment options for this disease were limited, but subsequently eight new drugs have received United States Food and Drug Administration approval for systemic treatment. The mainstay of treatment has proven to be oral tyrosine kinase inhibitors targeting the vascular endothelial growth factor (VEGF) and capitalizing on the inherent biology and reliance on angiogenesis for tumor growth and proliferation. Three oral TKIs targeting VEGF (sunitinib, pazopanib, and axitinib) have emerged as the primary options for most patients in the primary and second line of therapy. These drugs are relatively well tolerated and lead to objective response rates ranging from 25-48% across trials, however most patients ultimately develop drug resistance within a year on treatment, and second line options are characterized by diminishing clinical returns.[2] More durable disease control is desired.

The programmed death 1 (PD-1) inhibitor nivolumab was approved for use by the USFDA in November 2015 for patients with TKI refractory metastatic RCC. This drug is among the new class of immunotherapy drugs that block immune checkpoints to unleash an innate T-cell driven anti-tumor response. Nivolumab improved overall survival compared to the mammalian target of rapamycin inhibitor everolimus for patients with advanced RCC who had progressed on a prior TKI. Notably, though the overall response rate was 25% with nivolumab, nearly half of the patients who responded demonstrated prolonged or ongoing responses, which has been the hallmark of these agents.[3] Additionally, toxicities related to nivolumab, though somewhat unique compared to other classes of agents, were generally manageable.

### **1.2. Nivolumab**

#### **1.2.1. Mechanism of Action**

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed on antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumor responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumor growth.

### **1.2.2. Effects in Human**

The pharmacokinetics (PK), clinical activity, and safety of nivolumab have been assessed in approximately 70 clinical studies sponsored by BMS, ONO, or other partners. Across those studies, approximately 12,300 subjects have received nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies).

#### **Pharmacokinetics**

The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (V<sub>ss</sub>) is 8.0 L (30.4%), and geometric mean elimination half-life (t<sub>1/2</sub>) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

#### **Safety**

All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low-grade (Grade 1-2) with relatively few drug-related high-grade (Grade 3-4) AEs. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone.

Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy

#### **Clinical Activity**



Nivolumab has demonstrated clinical activity in NSCLC, melanoma, RCC, and cHL (approved indications) and other tumor types as monotherapy or in combination with ipilimumab. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard of care in subjects with advanced or metastatic melanoma, in subjects with advanced or metastatic NSCLC, and in subjects with advanced RCC[3-5]

### **Efficacy in patients with Renal Cell carcinoma**

Nivolumab monotherapy has demonstrated clinical benefit in subjects with advanced RCC, and has been approved for use in this population in the US, EU, and other countries.

Trial 6 was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS)  $\geq 70\%$  and patients were included regardless of their PD-L1 status. Trial 6 excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies

Patients were randomized to nivolumab (n=410) administered intravenously at 3 mg/kg every 2 weeks or everolimus (n=411) administered orally 10 mg daily. The median age was 62 years (range: 18 to 88) with 40%  $\geq 65$  years of age and 9%  $\geq 75$  years of age. The majority of patients were male (75%) and white (88%) and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (77%) were treated with one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 34% favorable, 47% intermediate, and 19% poor.

The major efficacy outcome measure was overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis). OS benefit was observed regardless of PD-L1 expression level. Nivolumab treated patients achieved an objective response rate (ORR) of 21.5%, compared to only 3.9% with everolimus. In patients who responded to nivolumab, the median duration of response was nearly 2 years (23 months), significantly longer than the 13.7 months from the everolimus group.

### **1.2.3. Rationale for using nivolumab flat dose of 480 mg in this study**

Nivolumab monotherapy has been extensively studied in a number of tumor types including NSCLC, melanoma, RCC, among others with body weight normalized dosing (mg/kg). Nivolumab PK and exposures of subjects have been characterized by population pharmacokinetic (PPK) analysis of data collected from these studies, together with PK data from several phase I, II, and III clinical studies of nivolumab monotherapy in solid tumors. PPK analyses have shown that the PK of nivolumab are linear, with dose proportional exposures over a dose range of 0.1 mg/kg to 10 mg/kg, and are similar across tumor types. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients. The initial approval of nivolumab was weight based at a dose of 3 mg/kg. However, taken together, the PK, safety, and efficacy data indicated that 240 mg nivolumab would provide similar outcomes to that of 3 mg/kg nivolumab and thus a flat dose of 240 mg every 2 weeks was approved by the USFDA and initially recommended for investigation in this study

Since study initiation, further data has provided updated dosing and schedule approval for nivolumab. As presented at the 2017 AACR Annual Meeting, assessments of safety across trials of various tumor types, along with quantitative clinical pharmacology analyses, revealed that a regimen of 480 mg administered every 4 weeks would have a <1% difference in the predicted chance of response.[6] This led to the approval of this dose and schedule across multiple tumor types, including RCC, and was approved by the USFDA on March 6, 2018.

*Please refer to Nivolumab Investigator's Brochure for detailed information on Nivolumab*

## **1.3. Axitinib (Inlyta)**

### **1.3.1. Mechanism of Action**

Axitinib is an orally bioavailable, small molecule tyrosine kinase inhibitor (TKI) that is approved for the treatment of patients with advanced renal cell carcinoma after failure of at least one prior TKI. It functions as a second generation TKI that impairs angiogenesis and subsequent tumor growth via inhibition of several vascular endothelial growth factor receptors (VEGFR) present on the endothelial cell, namely VEGFR 1, 2, and 3. More specifically, axitinib binds to the non-activated catalytic domain of the receptor and competitively inhibits adenosine

triphosphate. Preclinical cell-based receptor-binding assays have confirmed that axitinib is a potent and selective inhibitor of all three mentioned VEGFRs.

### 1.3.2. Pharmacokinetics

The population pharmacokinetic analysis pooled data from 17 trials in healthy subjects and patients with cancer. A two-compartment disposition model with first-order absorption and lag-time adequately describes the axitinib concentration-time profile.

Absorption and Distribution: Following single oral 5-mg dose administration, the median T<sub>max</sub> ranged from 2.5 to 4.1 hours. Based on the plasma half-life, steady state is expected within 2 to 3 days of dosing. Dosing of axitinib at 5 mg twice daily resulted in approximately 1.4-fold accumulation compared to administration of a single dose. At steady state, axitinib exhibits approximately linear pharmacokinetics within the 1-mg to 20-mg dose range. The mean absolute bioavailability of axitinib after an oral 5 mg dose is 58%.

Compared to overnight fasting, administration of axitinib with a moderate fat meal resulted in 10% lower AUC and a high fat, high-calorie meal resulted in 19% higher AUC. Axitinib can be administered with or without food.

Axitinib is highly bound (>99%) to human plasma proteins with preferential binding to albumin and moderate binding to  $\alpha$ 1-acid glycoprotein. In patients with advanced RCC (n=20), at the 5 mg twice daily dose in the fed state, the geometric mean (CV%) C<sub>max</sub> and AUC<sub>0-24</sub> were 27.8 (79%) ng/mL and 265 (77%) ng.h/mL, respectively. The geometric mean (CV%) clearance and apparent volume of distribution were 38 (80%) L/h and 160 (105%) L, respectively.

Metabolism and Elimination: The plasma half-life of axitinib ranges from 2.5 to 6.1 hours. Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Following oral administration of a 5-mg radioactive dose of axitinib, approximately 41% of the radioactivity was recovered in feces and approximately 23% was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in feces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

### 1.3.3. Clinical Activity

Axitinib was assessed in a randomized, open-label, multi-center phase III trial of patients with advanced RCC (99% clear cell) whose disease had progressed on or after treatment with 1 prior systemic therapy. Patients were randomized to

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receive axitinib (N=361) or sorafenib (N=362). Results revealed a statistically significant advantage for axitinib over sorafenib for the primary PFS endpoint, 6.7 (95% CI: 6.3, 8.6) vs 4.7 (95% CI: 4.6, 5.6) months, respectively ( $p < 0.0001$ ). However, there was no statistically significant difference between the treatment arms in the secondary overall survival (OS) endpoint, 20.1 (95% CI: 16.7, 23.4) vs 19.2 (95% CI: 17.5, 22.3) for axitinib and sorafenib, respectively. The ORR was reported as 19.4% (95% CI: 15.4, 23.9) for axitinib and 9.4% (95% CI: 6.6, 12.9) for sorafenib. [4]

In a separate phase III randomized trial, axitinib was also compared to sorafenib in the treatment naïve setting. It has not been compared to sunitinib or pazopanib in this setting in a prospective, randomized trial. In this study, patients were randomized (2:1) to receive axitinib (N=192) or sorafenib (N=96). In regards to the primary endpoint of median PFS, there was no significant difference between patients treated with axitinib or sorafenib (10.1 months vs 6.5 months, respectively), with stratified hazard ratio of 0.77, (95% CI 0.56, 1.05). [5] The safety of axitinib has been evaluated in 715 patients in monotherapy studies, which included 537 patients with advanced RCC. The data described below reflect exposure to axitinib in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib.

The most common ( $\geq 20\%$ ) adverse reactions observed following treatment with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.

Adverse Reactions Occurring in  $\geq 10\%$  of Patients who received axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia syndrome, weight decreased, vomiting, asthenia, constipation, hypothyroidism, cough, mucosal inflammation, arthralgia, stomatitis, dyspnea, abdominal pain, headache, pain in extremity, rash, proteinuria, dysgeusia, dry skin, dyspepsia.

Selected adverse reactions (all grades) that were reported in  $< 10\%$  of patients treated with axitinib included dizziness (9%), upper abdominal pain (8%), myalgia (7%), dehydration (6%), epistaxis (6%), anemia (4%), hemorrhoids (4%), hematuria (3%), tinnitus (3%), lipase increased (3%), pulmonary embolism (2%), rectal hemorrhage (2%), hemoptysis (2%), deep vein thrombosis (1%), retinal-vein occlusion/thrombosis (1%), polycythemia (1%), transient ischemic attack (1%), and RPLS ( $< 1\%$ )

*Please refer to Axitinib package insert for detailed information on Axitinib*

#### 1.4. Rationale for studying Axitinib and Nivolumab combination in RCC patients

In order to improve response rates and prolong disease control for patients with advanced renal cell carcinoma, new agents or strategies are needed. Checkpoint blockade remains promising, but the overall response rate must be improved to benefit a larger proportion of patients. Combination strategies offer the potential to increase response rates while still maintaining the durability of response associated with checkpoint blockade. Given the established efficacy and tolerability in RCC, pairing nivolumab with an oral VEGF TKI is a logical next step. A prior phase I, multi-arm study combined nivolumab with sunitinib or pazopanib in patients with advanced disease.[7] However, enhanced toxicity, namely elevations in liver transaminases, limited the clinical utility of these combinations. Axitinib, a TKI targeting VEGF and known to cause less hepatotoxicity as a single agent, may be a better partner. Reported results from the dose-finding portion of a phase Ib study combining axitinib with the PD-1 inhibitor pembrolizumab show the combination to be better tolerated, with only 2/11 patients experiencing grade 3 elevations in liver enzymes, neither of which needed to discontinue treatment for this reason.[8] Updated safety and efficacy results were published in 2018, revealing an ORR of 73%, with no signal of increased toxicity than would be expected with either drug alone.[9] Combining axitinib with nivolumab thus warrants clinical evaluation.

We propose a phase I/II trial of this combination first to test the safety of the combination, and then to explore efficacy in two RCC populations: patients who are treatment naïve (first line) and patients who have progressed after treatment with one or two prior treatments (second/third line). The initial phase I portion would include a small cohort of patients who have progressed on prior therapy in order to establish safety and determine a recommended phase II dose (RP2D). Once the RP2D is established, two parallel dose expansion arms including previously treated and treatment naïve patients, respectively, will be accrued simultaneously at the RP2D to get more robust safety data and secondarily explore efficacy in two homogenous populations.

#### 1.5. Correlative Testing

1. **Tumor biopsy assessment and translational studies:** Archival tissue from primary or metastatic lesions will be collected for retrospective assessment. Biomarker studies on tumor biospecimens including but not limited to tumor PD-L1 expression and assessments of tumor infiltrating lymphocytes will be carried out to interrogate for potential biomarkers and assess for potential mechanisms of sensitivity and resistance. Such results may help in the future development of this combination and appropriate selection of patients.
2. **Biomarkers analysis:** Blood will be collected during screening, once on treatment, and at the conclusion of study for various exploratory biomarker assessments and blood levels of various markers and cytokines to assess effects of this combination and interrogate potential biomarkers of response.

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## **2.0 Objectives**

### **2.1. Primary Objective**

- **Phase I:** To determine the safety and tolerability of the combination of axitinib and nivolumab in order to establish a recommended phase II dose (RP2D)
- **Phase II:** Assess the overall response rate of the combination in two separate cohorts of patients with treatment naïve and previously treated advanced RCC

### **2.2. Secondary Objectives**

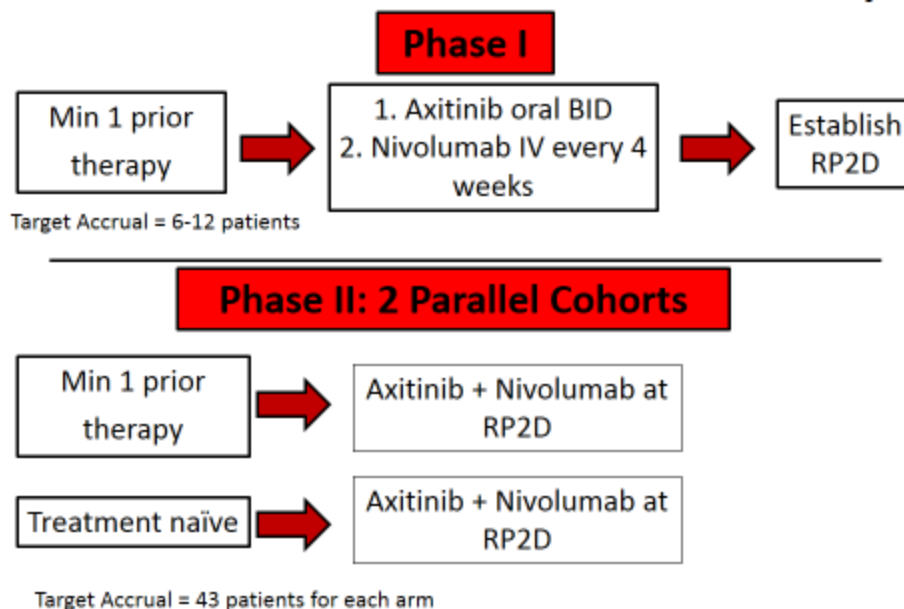
1. To evaluate the overall safety profile of the combination of axitinib and nivolumab
2. To assess the median progression free survival (PFS) and median overall survival (OS) of axitinib in combination with nivolumab in patients with advanced RCC
3. To explore sensitivity and resistance mechanisms to axitinib in combination with nivolumab in tumor and blood specimens
4. To explore the pharmacodynamic effect of axitinib in combination with nivolumab

## **3.0 Study Plan**

### **3.1. Description of Study Design, Population and Duration of Study Therapy**

This is a Phase I/II, open-label, multi-center study of axitinib in combination with nivolumab in patients with previously treated and untreated advanced RCC. This clinical study will be composed of a dose finding phase (Phase I) and two parallel dose expansion phases (Phase II). The dose finding phase will assess the safety of the combination and establish a recommended phase II dose (RP2D, the highest tested dose that is declared safe and tolerable by the Investigators and the Sponsor Investigator) in patients with advanced RCC who have received prior systemic therapy for metastatic disease. Phase II will evaluate the efficacy of the combination at the RP2D in two parallel expansion cohorts in both previously treated and treatment naïve patients.

## Schematic Overview for mRCC Phase I/II



### 3.1.1. Phase I

Phase I will be structured as a standard 3+3 phase I design, with increasing or decreasing doses of axitinib evaluated along with a standard, fixed dose of nivolumab based on DLTs. Six to twelve patients will be assessed during phase I until a RP2D is established.

#### Dose level for Phase I for Axitinib and Nivolumab

Dose Level (DL)	Axitinib	Nivolumab
+1	5 mg	480 mg
<b>0 (starting dose)</b>	<b>3 mg</b>	<b>480 mg</b>
-1	2 mg	480 mg

#### Decision Rules for Dose Escalation and Cohort Expansion

- See Appendix III for the dose escalation/de-escalation decision rules.
- Dose escalation will occur in a 3+3 dose escalation/de-escalation design
- Three patients will initially start at dose level 0 (DL0)
  - If 0 patients experience a DLT, the dose will be escalated one level and 3 more patients will be accrued at DL+1

- If 1 patient of the first 3 experiences a DLT, 3 more patients will be accrued at the same dose level. If no more DLTs, escalate to DL+1. If a second DLT occurs, deescalate to DL-1
- If 2 or 3 patients experience a DLT, deescalate to DL-1
- For patients escalated to dose level +1 (DL+1):
  - If 0-1 DLT is observed in the first 3 patients, 3 more patients will be accrued at this dose level. If after 6 patients accrued no more than 0-1 DLTs have been observed, DL+1 will be denoted the RP2D and the expansion cohorts may open at this dose level
  - If at any time 2 or more DLTs are observed at DL+1, deescalate back to DL0. If 6 patients have already been treated at this dose with 0-1 DLTs, declare this dose the RP2D. Otherwise 3 more patients will be accrued at that level and RP2D declared as below.
- Once 6 patients are accrued to dose level 0 (DL0):
  - If 0-1 DLT is observed, DL0 will be denoted the RP2D and the expansion cohorts may open at this dose level
  - If at any time 2 or more DLTs observed at this dose level, deescalate back to DL-1 and 3 more patients will be accrued at that level
- For patients deescalated to DL-1:
  - If 0-1 DLT is observed in the first 3 patients, 3 more patients will be accrued at this dose level. If after 6 patients accrued no more than 0-1 DLTs have been observed, DL-1 will be denoted the RP2D and the expansion cohorts may open at this dose level
  - If at any time 2 or more DLTs are observed at this dose level, the study will be stopped for toxicity

### **Determination of RP2D**

- The RP2D is the dose of axitinib and nivolumab in combination chosen for further clinical development. In the context of this study, the final dose level during the dose escalation phase that yields  $\leq 1$  DLTs will define the RP2D selection for further study in the dose expansion cohorts
- Further experience in the dose expansion cohorts may result in a modification of the RP2D to a dose lower than that chosen at the conclusion of the dose escalation.
- For axitinib, intra-patient dose escalation to higher doses may be permitted as outlined in the dose modification section of this protocol. However, the final RP2D will not be higher than axitinib 5 mg BID. Nivolumab dosing remains unchanged.
- If a patient does not receive at least 75% of the planned axitinib and two infusions of nivolumab within the DLT observation period for reasons other than study-drug related toxicity, another patient will be enrolled to replace that patient at the current dose level.

### **DLT Definition**

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- The DLT assessment window will be 28 days, starting from the first day of combination therapy (denoted C1D1) after the axitinib run-in period and will conclude after 28 days (4 weeks). One cycle is denoted as 28 days so the end of the DLT window may coincide with the conclusion of cycle #1. If the second dose of nivolumab on C#2 is delayed for any reason other than a DLT, the DLT window period would still conclude after 28 days
- Toxicity will be evaluated according to the NCI CTCAE, version 4.03
- A DLT will be defined as any of the following AEs that is “possibly” related to one or both drugs during the DLT assessment window period

<b>Hematologic</b>	Grade 4 neutropenia defined as $< 500/\text{mm}^3$ lasting $> 5$ days in duration
	Febrile neutropenia defined as $\text{ANC} < 1000/\text{mm}^3$ with a single temperature of $> 38.3^\circ\text{C}$ ( $101^\circ\text{F}$ ) or a sustained temperature of $\geq 38^\circ\text{C}$ ( $100.4^\circ\text{F}$ ) for more than one hour
	Grade $\geq 3$ neutropenic infection
	Grade 4 thrombocytopenia (platelets $< 25,000$ cells/ $\text{mm}^3$ ) or Grade $\geq 3$ thrombocytopenia with bleeding
<b>Non-Hematologic</b>	Grade $\geq 3$ nausea, vomiting, or diarrhea that does not improve to grade $< 2$ within 72 hours despite maximal medical therapy
	Grade $\geq 3$ rash that does not improve to grade $< 2$ within 7 days despite maximal medical therapy, or at any time involves desquamation, mucosal involvement, or requires initiation of systemic steroids
	Grade $\geq 3$ drug-related uveitis, iritis, episcleritis, eye pain, or blurred vision
	Grade $\geq 3$ hypertension despite maximal medical therapy
	Any other grade $\geq 3$ non-laboratory or symptom-based toxicity not improved to grade $< 3$ despite maximal medical or supportive therapy after 7 days
	Any grade encephalitis or Grade $\geq 2$ pneumonitis that are at least possibly related to nivolumab

<b>Laboratory</b>	Grade $\geq 2$ AST and/or ALT ( $> 3\times$ ULN) in combination with total bilirubin $> 2\times$ ULN
	Grade $\geq 3$ non-hematologic laboratory value that does not return to grade 1 within 7 days despite maximal medical therapy OR that requires hospitalization
<b>Other</b>	Inability to complete at least 75% of axitinib dosing within the 4-week DLT observation period due to treatment-related toxicity
	$> 2$ dose reductions of axitinib during the DLT window

### 3.1.2. Phase II

Phase II will include 43 patients at the RP2D in each arm of treatment naïve or patients who have received prior TKIs. In all patients, treatment with study drugs will continue until confirmed disease progression, patient withdrawal of consent, patient lost to follow up, unacceptable toxicity, or if the study is terminated by the Sponsor. Patients may remain on both axitinib and nivolumab if clinically benefitting for up to 12 months. At that time patients may continue on one or both medications at the discretion of the treating clinician and with agreement by the patient. The trial will end at the completion of 24 months of therapy, at which point patients can decide with their treating clinician how to proceed. Patients who elect to stop one drug after one year and who develop progression of disease may elect to be retreated at that time as part of the trial. Nivolumab, if stopped at one year, will be provided by the study in those instances, but up to a maximum total of 24 months of treatment. If either drug is stopped due to toxicity or investigator's decision, the patient may continue to receive the other drug in the combination.

Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline, then at 8 weeks after combination and every 3 cycles thereafter, using RECIST version 1.1. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the end of treatment/withdraw from study (if not done in the previous 6 weeks). Patients may be treated beyond radiologic progression if the patient is deemed to be clinically benefitting by the study treatment, however two assessments documenting progression will necessitate the patient be removed from the study. Primary assessments will be performed with computed tomography (CT) of the chest, abdomen and pelvis. Bone scintigraphy will be performed at baseline, then with every subsequent restaging period ONLY if bone metastases are documented or suspected. Brain CT or MRI scans are required at

baseline when there are known or suspected brain metastases. In case of no known or suspected brain metastases, brain imaging is not needed at any time.

Overall survival will be assessed every 3 months for the first 2 years, then every 6 months for 2 years, and then annually.

#### **4.0 Patient Selection Inclusion & Exclusion**

##### **4.1. Inclusion Criteria**

- 4.1.1 Histologically or cytologically confirmed advanced RCC with any clear cell component. 100% sarcomatoid is permissible.
- 4.1.2 Archival tumor biospecimen (when available) must be procured for correlative evaluation. If tumor tissue is not available or accessible despite good faith efforts, patient may still be treated on study.
  - Formalin fixed, paraffin embedded [FFPE] tissue block(s) or at least 12 unbaked, unstained slides are required. Tissue samples taken from a metastatic lesion prior to the start of screening are acceptable.
- 4.1.3 At least one measureable lesion as defined by RECIST version 1.1.
- 4.1.4 Age > 18 years.
- 4.1.5 ECOG performance status 0 or 1
- 4.1.6 Adequate bone marrow, kidney, and liver function as defined below:
  - WBC  $\geq 2000/\mu\text{L}$
  - Neutrophils  $\geq 1500/\mu\text{L}$
  - Platelets  $\geq 100 \times 10^3/\mu\text{L}$
  - Hemoglobin  $> 9.0 \text{ g/dL}$
  - Serum creatinine  $\leq 1.5 \times \text{ULN}$  or creatinine clearance ( $\text{CrCl}$ )  $\geq 40 \text{ mL/min}$  (if using the Cockcroft-Gault formula below):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

- AST/ALT  $\leq 3 \times \text{ULN}$
- Total Bilirubin  $\leq 1.5 \times \text{ULN}$  (except subjects with Gilbert Syndrome, who can have total bilirubin  $< 3.0 \text{ mg/dL}$ )

- 4.1.7 No evidence of pre-existing uncontrolled hypertension as documented by 2 baseline blood pressure (BP) readings taken at least 1 hour apart. The baseline systolic BP readings must be  $\leq 150$  mm Hg, and the baseline diastolic BP readings must be  $\leq 90$  mm Hg
- 4.1.8 Patients enrolled to the prior treatment arm of the expansion cohort must have been exposed to a TKI for metastatic disease. Exposure to TKI as part of (neo)adjuvant treatment that completed within 1 year of study qualifies as prior exposure as well.

## **4.2. Exclusion Criteria**

- 4.2.1 Prior therapy with axitinib
- 4.2.2 Prior systemic therapy directed at advanced RCC is not allowed for patients enrolled to the expansion cohort, treatment naïve arm. If prior (neo)adjuvant treatment given as part of a clinical trial, this would be allowed as long as last dose was  $> 1$  year prior to start of treatment
- 4.2.3 Patients enrolled to the prior treatment arm of the dose escalation cohort must not have received anti-cancer therapy less than 14 days prior to the first dose of study drug or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug.
- 4.2.4 Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). Prior high dose interleukin-2 is allowed and patients who received this as their only prior line of treatment for metastatic disease may be included in the treatment naïve group.
- 4.2.5 Patients are excluded if they have active, symptomatic brain metastases or leptomeningeal metastases. Subjects with known brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for four weeks (after treatment is complete and within 28 days prior to study drug administration.
- 4.2.6 Second malignancy requiring active systemic treatment
- 4.2.7 Diagnosis of immunodeficiency
- 4.2.8 Active, known or suspected autoimmune disease. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger
- 4.2.9 Patients have a condition requiring systemic treatment with either corticosteroids ( $> 10$  mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses  $> 10$  mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

- 4.2.10 Major surgery <4 weeks or radiation therapy <2 weeks of study entry. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been irradiated.
- 4.2.11 Gastrointestinal abnormalities including:
- Inability to take oral medication;
  - Requirement for intravenous alimentation;
  - Prior surgical procedures affecting absorption including total gastric resection;
  - Treatment for active peptic ulcer disease in the past 6 months;
  - Active gastrointestinal bleeding as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
  - Malabsorption syndromes.
- 4.2.12 Evidence of inadequate wound healing.
- 4.2.13 Active bleeding disorder or other history of significant bleeding episodes within 30 days before study entry.
- 4.2.14 Known prior or suspected hypersensitivity to study drugs or any component in their formulations.
- 4.2.15 Current use or anticipated need for treatment with drugs or foods that are known strong CYP3A4/5 inhibitors including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.
- 4.2.16 Current use or anticipated need for treatment with drugs that are known strong CYP3A4/5 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.
- 4.2.17 As there is potential for hepatic toxicity with nivolumab, drugs with a predisposition to hepatotoxicity should be used with caution in patients treated with nivolumab-containing regimen.
- 4.2.18 Known hepatitis B virus (HBV) or hepatitis C virus (HBV) infection.
- 4.2.19 Known history of human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- 4.2.20 History of any of the following cardiovascular conditions within 12 months of screening:
- Myocardial infarction
  - Unstable angina pectoris
  - Cardiac angioplasty or stenting
  - Coronary/peripheral artery bypass graft
  - Class III or IV congestive heart failure per New York Heart Association
  - Cerebrovascular accident or transient ischemic attack

4.2.21 History of deep vein thrombosis or pulmonary embolism within 6 months of screening. Patients who are currently taking anticoagulation therapy for a prior history (> 6 months from screening) of thrombosis may still be eligible.

4.2.22 Pregnant or breast feeding. Refer to section 4.4 for further detail.

### **4.3. Inclusion of Women and Minorities**

Men and women, regardless of race, ethnic group or sexual orientation are eligible for this study.

### **4.4. Pregnancy**

- Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks after the last dose of investigational drug.
- Women of childbearing potential must have a negative serum pregnancy test within 72 hours of beginning study treatment.
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year and will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product.
- Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) as well as azospermic men do not require contraception

WOCBP is defined as follows: Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea  $\geq$  12 consecutive months, or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be WOCBP.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In addition, men enrolled on this study should understand the risks to any sexual partner of childbearing potential.

Should a woman or female partner of a male study participant become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

#### 4.5. Patient Registration

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the study monitor at: [FCCC.MONITOR@fcc.edu](mailto:FCCC.MONITOR@fcc.edu). Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

Following registration, participants must begin protocol treatment within 14 calendar days of registration. Issues that would cause treatment delays must be discussed with the Sponsor- Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional registration questions, please email [FCCC.MONITOR@fcc.edu](mailto:FCCC.MONITOR@fcc.edu) or call (215) 728-5544.

The study monitor or their designee will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

**Exceptions to the current registration policies will not be permitted.**

#### 5.0 Treatment Plan

##### Phase I

During the phase I portion, patients will be treated with 3 mg of axitinib orally (PO) twice daily (BID) , with or without food, for a seven day lead-in period prior to combination therapy (1<sup>st</sup> day of dosing axitinib during lead-in will be denoted day -7 and proceed to day -1 as last day of axitinib alone). Dose for lead-in period will be same as assigned dose level. Patients will then start treatment with nivolumab in addition to continuing daily axitinib dosing (1<sup>st</sup> day of combination treatment denoted cycle 1, day 1 [C1D1]). Nivolumab will be administered as a 30-minute intravenous (IV) infusion at 480 mg every 4 weeks. Patients will be accrued in a standard 3+3 design. If that is deemed safe, dose escalation of axitinib to a standard dosing of 5 mg PO BID (DL+1 as outlined in section 3.1.1 above) will be evaluated. Nivolumab dosing will remain unchanged at 480 mg. The combination of axitinib with nivolumab that meets the pre-specified definition of safety outlined in the protocol will be denoted the RP2D and will move forward for further study. A patient who is unable to start at the assigned Cycle 1 Day 1 dose level after the lead-in period will not be evaluable for DLTs but may remain in the study and will be evaluated for safety and efficacy, though they will be replaced for the primary endpoint.

**Phase II**

During the phase II portion, patients will be treated at the RP2D determined in the Phase I portion of the study. There will be two parallel dose expansion phase cohorts: one for patients with prior TKI exposure and a second for treatment naïve patients. In all patients, treatment with study drugs will continue until confirmed disease progression, patient withdrawal of consent, patient lost to follow up, unacceptable toxicity, or if the study is terminated by the Sponsor. Patients may remain on both axitinib and nivolumab if clinically benefitting for up to 12 months. At that time patients may continue on one or both medications at the discretion of the treating clinician and with agreement by the patient. See section 3.1.2 above for discussion of options at one year and total length of treatment allowed.

**5.1. Treatment Regimen**

Regimen description					
Agent	Premedications, precautions	Dose	Route	Schedule	Cycle Length
Nivolumab	No premedication	480 mg	IV over 30 min (- 5/+ 30 min)	Day 1 of each cycle	4 weeks (28 days)
Axitinib	Swallow whole with a glass of water	2 mg or 3 mg or 5 mg (see dose level chart)	PO	BID, continuous dosing	

**5.2. Nivolumab Administration**

Subjects may be dosed no less than 26 days or more than 30 days from the previous dose of drug. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to infusion reaction guidelines described in Appendix I.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection must be diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentration as low as 0.35 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.



### 5.2.1. Preparation and Administration

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.  
*Note: Mix by **gently** inverting several times. **Do not** shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall.
3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.

**Note: Nivolumab infusion concentration must be approximately 0.35 mg/mL.**

*Note: It is not recommended that so-called “channel” or tube systems are used to transport prepared infusions of nivolumab.*

4. Attach the IV bag containing the nivolumab solution to the infusion set and filter.
5. Nivolumab should be infused over 30 minutes, -5/+ 30 minutes. For patients who require rate reduction to accommodate infusion reactions, longer infusion time would be permitted and advised.
6. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

### 5.3. Axitinib Administration

Administer axitinib doses approximately 12 hours apart with or without food. Axitinib should be swallowed whole with a glass of water. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

### 5.4. Concomitant Medications, Supportive Care, Excluded Therapies and Restrictions

#### 5.4.1. Permitted Medications

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

#### 5.4.2. Prohibited Medications

Medications specifically prohibited in the exclusion criteria are not allowed during the study. If there is a clinical indication for medications specifically prohibited during the trial, discontinuation from the study may be required.

As there is potential for hepatic toxicity with nivolumab, drugs with a predisposition to hepatotoxicity should be used with caution during the study.

In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1. Therefore concomitant use of strong CYP3A4/5 inhibitors and strong CYP3A4/5 inducers should be avoided.

#### **Strong CYP3A4/5 Inhibitors:**

The concomitant use of strong CYP3A4/5 inhibitors should be avoided. When such a medicine is needed, selection of an alternative with no or minimal CYP3A4/5 inhibition potential is desired where possible. Please see a partial but not necessarily complete list of drugs to avoid below:

- Ketoconazole
- Itraconazole
- Clarithromycin
- Atazanavir,
- Indinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Telithromycin
- Voriconazole

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, axitinib dosing should be decreased approximately by half, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration vs time curve (AUC) to the range observed without inhibitors.

Subsequent doses can be modified as needed by the treating clinician based on individual safety and tolerability. If and when the strong inhibitor is discontinued, the axitinib dose should be returned (after 3 – 5 half-lives of the inhibitor) to the dose used prior to initiation of the strong CYP3A4/5 inhibitor.

**CYP3A4/5 Inducers:**

The concomitant use of strong CYP3A4/5 inducers should be avoided. When such a medicine is needed, selection of an alternative with no or minimal CYP3A4/5 induction potential is desired where possible. Please see a partial but not necessarily complete list of drugs to avoid below:

- Rifampin
- Dexamethasone
- Phenytoin
- Carbamazepine
- Rifabutin
- Rifapentin
- Phenobarbital
- St. John's Wort

**Moderate CYP3A4/5 inducers:**

Moderate CYP3A4/5 inducers may also reduce the plasma exposure of axitinib and should be avoided when possible. Examples are listed below and should not be considered complete:

- Bosentan
- Efavirenz
- Etravirine
- Modafinil
- Nafcillin

## **5.5. Duration of Therapy**

In the absence of treatment delays due to adverse events, treatment will continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- If nivolumab held > 8 weeks with exceptions described in section 6.3.3
- Patient required > 2 dose reductions of axitinib
- Patient becomes pregnant
- Patient lost to follow up
- Patient decides to withdraw from the study or
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

- Study is terminated by the Sponsor
- Patient completes therapy as specified in section 3.1.2
- Non-compliance

## 5.6. Treatment beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria determined by the investigator:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Stable performance status

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).

A radiographic assessment/ scan should be performed  $\geq 6$  weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

For the subjects who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions that become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

### 5.7. Duration of Follow up

Patients will be followed every 3 months for the first 2 years, then every 6 months for 2 years, and then annually for survival. Subjects who discontinue treatment for reasons other than disease progression should continue to have radiographic assessments of disease at least every 12 weeks until documented disease progression. Patients removed from study for unacceptable adverse events that are related to the study treatment will be followed until resolution or stabilization of the adverse event.

## 6.0 Dose Modifications

### 6.1. Dose Level Adjustment Table(s)

Dose level	Axitinib Dose	Nivolumab Dose
+1	5mg BID	480 mg
0	3mg BID	480 mg
-1	2mg BID	480 mg
-2	1 mg BID	480 mg

### 6.2. Axitinib Dose Modifications

#### 6.2.1. Axitinib Intra-Patient dose increase:

For the phase II portion of the study, or in phase I once patients complete the DLT assessment phase, those patients who tolerate axitinib exceptionally well may undergo further dose escalations of axitinib if deemed indicated by the treating clinician and meeting the following criteria:

- At least two consecutive weeks with no adverse reactions > Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE])
- Blood pressure  $\leq$  150/90 and receiving  $\leq$  2 anti-hypertensive medications

In these instances, patients may have their dose increased. When the initial dose is 3 mg BID, they may increase to 5 mg BID. When they start at, or escalate to, 5 mg BID, the dose may be increased to 7 mg BID, and further to 10 mg BID using the same criteria.

#### 6.2.2. Axitinib dose modifications due to toxicity:

Axitinib dose modifications or reductions due to toxicity may occur at any time on study if deemed necessary. Dose interruptions with or without dose reductions may occur as indicated. Patients may undergo two dose reductions of axitinib from the dose level at which they initiated treatment. If further dose reduction recommended after this, patients should discontinue axitinib. If they are otherwise clinically benefitting and dose discontinuation achieves the desired recovery of toxicity, patients may remain on treatment with nivolumab. However, if this occurs in the DLT window, this would be considered a DLT.

<b>Toxicity Class</b>	<b>NCI CTCAE Severity Grade</b>	<b>Axitinib</b>
<b>Hypertension</b>	BP $\geq$ 140 systolic or $\geq$ 90 diastolic but $<$ 160 systolic or $<$ 100 diastolic on at least 2 BP readings $>$ 1 hour apart	Start new, increase, or add additional anti-hypertensive medication and continue at same dose level.  If on maximal anti-hypertensive medical therapy, reduce dose by 1 level
	Recurrent grade 2 (140-160 systolic and 90-100 diastolic) after previous dose reduction and on maximal anti-hypertensive therapy	Dose reduce axitinib a second dose level
	Systolic BP reading $\geq$ 160 mmHg OR diastolic BP $\geq$ 100 mmHg of at least 2 BP readings $>$ 1 hour apart	Withhold dose of axitinib until BP $\leq$ 140/90 and adjust anti-hypertensive medications as appropriate.  Reduce axitinib dose by 1 dose level and resume.
<b>Hematologic Abnormalities</b>	Grade 1-3	Continue at the same dose level
	Grade 4 (except for lymphopenia not associated with infection)	Withhold until recovery to $\leq$ grade 2 then reduce dose by 1 dose level and resume.
<b>Liver Function test Abnormalities (AST, ALT, Bilirubin)</b>	Grade 1	Continue at the same dose level
	Grade 2	Withhold until grade $<$ 2 or baseline and restart at the same dose level.

	Recurrent Grade 2 or Grade 3-4	Withhold until grade < 2 or baseline and reduce by one dose level.
<b>Non-Hematologic Laboratory abnormalities</b>	Grade 1-2	No Change
	Grade 3 - Asymptomatic	May continue at same dose level or reduce 1 dose level as deemed appropriate by treating clinician.
	Grade 3 - Symptomatic	Treat as appropriate with supportive measures and reduce dose by 1 dose level.
	Grade 4	Hold treatment until recovery to $\geq$ grade 2, then reduce by 1 dose level and resume treatment.
<b>Diarrhea</b>	Grade 1-2	Continue at the same dose level. Add supportive medicines as needed.
	Grade 3	Hold until grade $\leq$ grade 2 and reduce by 1 dose level
	Grade 4	Discontinue medication
<b>Pneumonitis</b>	Grade 1-2	No change
	Grade 3-4	Discontinuation
<b>Hypo/Hyperthyroidism</b>	Grade 1-2	No change
	Grade 3	Continue at the same dose level. Add supportive medicines as needed. May decrease one dose level if deemed appropriate by treating clinician.
	Grade 4	Hold drug until recovery to < grade 2, treat as appropriate, and resume at dose reduced one level.

### 6.3. Nivolumab Dose Modifications

Dose reductions or dose escalations are not permitted. Missed doses are not to be made up. If treatment is delayed or interrupted for > 8 weeks, the subject must be permanently discontinued from study therapy unless discussed with medical monitor and study team for exception due to extenuating circumstances.

#### 6.3.1. Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab). However, if in opinion of treating clinician, drug-related AE is most likely a result of one drug, that drug may be held and the other drug may continue as planned. If held drug is axitinib, it can be restarted as per improvement in AE per below guidelines at any point in treatment cycle. If the held drug is nivolumab, it should be skipped and not made up and if AE resolves per criteria should be restarted at start of next cycle

**Nivolumab administration should be delayed for the following:**

- Any Grade  $\geq 2$  non-skin, drug-related immune related AE, with the following exceptions:
  - Grade 2 drug-related fatigue does not require a treatment delay
  - Grade 2-4 endocrine abnormalities such as hypothyroidism, hyperthyroidism, or hyperglycemia that may be treated with appropriate supportive therapy or hormonal replacement do not require a treatment hold or delay
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia or leukopenia does not require dose delay.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade  $\geq 2$  toxicity.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade  $\geq 3$  toxicity.
  - Any Grade  $\geq 3$  drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Investigator should be consulted for such Grade  $\geq 3$  amylase or lipase abnormalities.
  - Any grade endocrine abnormalities attributed to nivolumab but that can be managed solely with hormone replacement therapy (physiologic steroids,



levothyroxine, insulin, etc) do not require dose delay, but decision to continue or resume treatment if held may be left to the treating investigator in discussion with the patient

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

### **6.3.2. Criteria to Resume Treatment**

Subjects may resume treatment with study Nivolumab when the drug-related AE(s) resolve to Grade  $\leq 1$  or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper within 6 weeks may be eligible for retreatment if treating clinician allows
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment if investigator allows

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. In regards to axitinib, that would mean the next day regardless of point in cycle. For nivolumab that would mean day one of next cycle.

### **6.3.3. Criteria for Discontinuation**

Nivolumab should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT  $\geq$  Grade 3
      - Total bilirubin  $\geq$  Grade 3
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 lymphopenia or leukopenia
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Investigator
- Any dosing interruption lasting > 8 weeks with the following exceptions:
  - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 8 weeks, the Sponsor-Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
  - Dosing interruptions or delays lasting > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the Sponsor-Investigator. Prior to re-initiating treatment in a subject with a dosing

interruption lasting > 8 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the site Investigator or Sponsor-Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

#### 6.3.4. Recommended Dose Modification for Nivolumab

Toxicity	Severity Grade	Nivolumab
Colitis or Diarrhea	Grade 2	Withhold dose <sup>a</sup>
	Grade 3	Withhold dose <sup>a</sup>
	Grade 4	Permanently discontinue
Pneumonitis	Grade 2	Withhold dose <sup>a</sup>
	Grade 3 or 4	Permanently discontinue
Hepatitis	Grade 2 AST or ALT or total bilirubin	Withhold dose <sup>a</sup>
	Grade 3 or 4 AST/ALT/ total bilirubin	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose <sup>a</sup>
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2	Withhold dose, but may consider restarting if stable with appropriate replacement
	Grade 3 or 4	Withhold dose, but may consider restarting if stable with appropriate replacement
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose, may consider restarting if adequate glucose control instituted. Patients who have known type 2 diabetes at study onset do

		not need to be held for grade 3 hyperglycemia
	Grade 4 hyperglycemia	Withhold dose, may consider restarting if adequate glucose control instituted
Nephritis and Renal Dysfunction	Grade 2 or 3 serum creatinine	Withhold dose <sup>a</sup>
	Grade 4 serum creatinine	Permanently discontinue
Rash	Grade 3	Withhold dose <sup>a</sup>
	Grade 4	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose <sup>a</sup>
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction - First occurrence - Recurrence of same Grade 3 adverse reactions	Withhold dose <sup>a</sup> Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

<sup>a</sup> Resume treatment when adverse reaction returns to Grade 0 or 1.

## 7.0 **Study Agent Information**

### 7.1. **Nivolumab**

#### 7.1.1. **Product description**

**Product Description:(Other names = MDX-1106, ONO-4538, anti-PD-1)**

<b>Product Description and Dosage Form</b>	<b>Potency</b>	<b>Primary Packaging (Volume)/ Label Type</b>	<b>Secondary Packaging (Qty) /Label Type</b>	<b>Appearance</b>	<b>Storage Conditions (per label)</b>
Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100 mg/Vial (10 mg/mL). 40 mg/vial (10 mg/mL)	10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals/open label	Carton of 5 or 10 vials (100 mg vials) or Carton containing 2 x 100 mg vials and 1 x 40 mg vial/open label	Clear to opalescent, colorless to pale yellow liquid. May contain particles	<b>BMS-936558-01 Injection</b> must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

\*Nivolumab may be labeled as BMS-936558-01 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

**7.1.2. Availability**

Nivolumab used in this study will be supplied by Bristol Myers Squibb.

**7.1.3. Recommended prepared drug storage and use condition**

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20° to 25°C, 68° to 77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

**7.2. Axitinib****7.2.1. Product description**

1 mg tablets are red film-coated, oval tablets debossed with “Pfizer” on one side and “1 XNB” on the other; available in bottles of 180.

5 mg tablets are red film-coated, triangular tablets debossed with “Pfizer” on one side and “5 XNB” on the other; available in bottles of 60

### **7.2.2. Availability**

Axitinib will be ordered through usual mechanisms as standard of care as an FDA-approved drug for this indication (TKI-refractory). For patients treated in the treatment-naïve cohort, the NCCN guidelines list axitinib as an acceptable alternative for 1<sup>st</sup> line therapy for selected patients.

### **7.2.3. Storage requirements**

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

## **7.3. Drug Ordering, Storage and Handling**

Following submission and approval of the required regulatory documents, participation in the study initiation meeting and receipt of the site activation letter from the IST Regulatory Specialist, the initial order may be placed. Drug order forms and ordering procedure will be presented at the site initiation meeting.

## **7.4. Destruction of Drug**

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs unless otherwise specified by sponsor.

## **7.5. Records to be kept at Site; Dispensing and Accountability**

It is the responsibility of the Sponsor-Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).

## **8.0 Correlative /Special Studies**

We will collect archival tumor tissue (when available) for all patients for biomarker exploration as well as serum and plasma samples at three time points on study.

## **8.1. Biopsy Specimen Analysis**

### **8.1.1. Outcome measure**

Tissue will be collected at baseline from archival specimens or fresh biopsy samples, when available, to assess for markers that may predict for response that may include but are not limited to: PD-L1 expression, tumor infiltrating lymphocytes, markers of interferon signaling

### **8.1.2. Assessment, method of assessment, timing of assessment**

This may include but is not limited to immunohistochemistry, NanoString, and next generation sequencing

### **8.1.3. Site(s) performing correlative study**

Fox Chase Cancer Center will perform the analysis. All sites will collect and ship the samples to Fox Chase Cancer Center.

## **8.2. Biomarker Analysis**

### **8.2.1. Outcome measure**

Blood will be collected to analyze for levels of various cytokines, chemokines and other biomarkers that may predict for response or resistance.

### **8.2.2. Assessment, method of assessment, timing of assessment**

This may include but is not limited to- specific antibody assays, cell free DNA

Timing of assessment- blood will be collected at three time points:

1. Lead-in day -7
2. Prior to Cycle 2 Day 1
3. End of treatment

### **8.2.3. Site(s) performing correlative study**

Fox Chase Cancer Center will perform the analysis. All sites will collect and ship the samples to Fox Chase Cancer Center.

**9.0 Study Calendar**

Study Phase	Pre-Study <sup>b</sup>	Lead-In Phase	Treatment (1 cycle is 28 days)			End of Treatment	Follow-Up	
			Cycle 1	Cycle 2 and beyond			Safety Follow-up	Follow-up
Treatment Days		Day -7 to 0 (+3 days)	Day 1	Day 15	Day 1 (+/-2)	At time of Discon	100 days post Discon	
Informed consent & HIPAA	X							
Medical history	X							
Physical exam <sup>N</sup>	X	X	X	X	X			
Weight	X			X				
Vital signs (T, P, R, BP) <sup>a</sup>	X	X	X	X	X			
Performance status	X	X	X	X	X	X		
CBC w/diff, plts	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X		
Serum chemistry <sup>e</sup>	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X		
Thyroid (TFTs)	X		X <sup>f</sup>					
β-HCG <sup>d</sup>	X		X <sup>f</sup>					
Urinalysis	X		X <sup>f</sup>					
Pulse Oximetry <sup>g</sup>	X		X		X			
Concurrent meds	X	X-----X <sup>o</sup>						
Adverse event evaluation		X-----X <sup>p</sup>						
Disease Assessment <sup>h</sup>	X	After 8 weeks of the combination (+/- 7 days) and then every 3 cycles (+/- 7 days)				X <sup>j</sup>		X <sup>k</sup>
Bone Scan (if indicated) <sup>i</sup>	X (if indicated)	After 8 weeks of the combination (+/- 7 days) and then every 3 cycles (+/- 7 days)				X <sup>j</sup>		X <sup>k</sup>
Survival <sup>l</sup>								X
Blood collection for correlative studies <sup>m</sup>		X			C2D1 only	X		
Archival Tumor Tissue	X							
Axitinib		X						
Nivolumab			X		X <sup>c</sup>			
<p><b>a:</b> 2 baseline blood pressure (BP) readings will be taken at least 1 hour apart. The baseline systolic BP readings must be ≤ 150 mm Hg, and the baseline diastolic BP readings must be ≤ 90 mm Hg</p> <p><b>b:</b> Pre-study H&amp;P and all labs must be ≤ 28 days prior to registration. Tumor measurements and radiologic evaluations must be ≤ 28 days prior to registration. Pre-study assessments may be used for lead-in day -7 if completed ≤ 28 days from day one of treatment.</p>								



- c: Nivolumab is given on day 1 of every cycle.
- d: Serum pregnancy test (women of childbearing potential) must be completed  $\leq 72$  hours before beginning treatment.
- e: Following Laboratory test must be done prior to each dose of Nivolumab: CBC w/ differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose
- f: TSH should be done every 2 cycles starting cycle 1, with free T4 and free T3 done only if TSH is abnormal. B-HCG, if applicable, and urinalysis are also to be conducted every 2 cycles starting with cycle 1, ie, C1, C3, C5...etc (odd numbered cycles).
- g: Oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at pre-study visit and prior to dosing with Nivolumab on day 1 of each cycle.
- h: Imaging modality in order of preference is as follows: 1. CT Chest, Abdomen, and Pelvis with contrast 2. Non-contrast CT of the chest, and MRI of the abdomen/pelvis 3. CT Chest, Abdomen, and Pelvis without contrast. The same imaging modality should be used at baseline and follow-up.
- i: Bone scintigraphy will be performed at baseline then with every subsequent restaging period only if bone metastases are documented or suspected. Bone scans are not needed at any time if no known or suspected bone metastases.
- j: Tumor measurements including CT/bone scan/MRI will be done at the end of treatment visit only if not done in the previous 6 weeks
- k: Subjects who discontinue treatment for reasons other than disease progression should continue to have radiographic assessments of disease at least every 12 weeks until documented disease progression.
- l: Follow-up every 3 months for the first 2 years, then every 6 months for 2 years, then annually for study survival.
- m: Blood samples will be collected at lead-in phase (time 1), prior to C2D1 (time 2) and at end of treatment (time 3). Sera, plasma and whole blood will be collected. Sera- 1(10mL) red top tube clotted sample. Plasma and whole blood control- 1(10mL) EDTA tube.
- n. Physical exam must be done day 1 of each cycle..
- o: During safety follow-up period, any new cancer treatment and concomitant medicines used to treat irAEs will be reported
- p: During safety follow-up period, any new or ongoing protocol treatment-related AEs will be reported

## **10.0 Adverse Events**

### **10.1. Adverse Event Definition**

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

### **10.2. Serious Adverse Event (SAE)**

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and a new cancer are not always serious by regulatory definition, these events must be handled as SAEs.

**Potential drug induced liver injury (DILI) is defined as:**

- 1) ALT or AST elevation > 3 times upper limit of normal (ULN)  
AND

- 2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)  
AND
- 3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

### **Definition of Overdose:**

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

### **10.3. Severity Rating**

The site Investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

### **10.4. Attribution/Relationship to study drug**

1. Definite – clearly related
2. Probable – likely related
3. Possible – may be related
4. Unlikely – doubtfully related
5. Unrelated – clearly not related

### **10.5. Expectedness**

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or
2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.

## **10.6. Recording and Reporting Responsibilities**

### **10.6.1. Investigative Site Recording Responsibilities:**

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.
2. All AEs and SAEs will be recorded in the “AE case report forms” (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient’s outcome will be recorded in the CRF. All events will be recorded on case report forms during the treatment period. All new, or on-going protocol treatment-related AEs will be followed for a minimum of 100 days following the last dose of study treatment. All treatment-related AEs should be followed to resolution or stabilization.
3. All reportable SAEs will be recorded on the FDA MedWatch form 3500a. After submitting the initial report it may be necessary to submit follow up reports to the OCR should the event require further investigation.

### **10.6.2. Investigative Site Reporting Responsibilities:**

1. The site Investigator/ site is responsible to report all SAEs that occur on or after the first day of study treatment to the IST Regulatory Specialist within 24 hours of becoming aware of the event. All subsequent SAEs must be reported for up to 100 days after the last treatment.

Each site Investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent email to the IST Regulatory Specialist at **SAE.FCCC@fccc.edu**.

2. If the site Investigator or site IRB feels the event warrants a revision to the informed consent that was not already initiated by the OCR, draft revisions will be made in track changes and submitted to the OCR for consideration. Any consent revisions must receive OCR approval **prior** to submission to the IRB.
3. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation with the Sponsor Investigator
4. If the results of an investigator or OCR investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.
5. Copies of all related correspondence and reporting documents must be submitted to the IST Regulatory Specialist and will be maintained in the trial master file.

**Participating sites should report events to:**

IST Regulatory Specialist  
 Fox Chase Cancer Center  
 Office of Clinical Research  
 333 Cottman Avenue  
 Philadelphia, PA 19111  
 Phone 215-214-1439  
 SAE.FCCC@fccc.edu

**10.6.3. OCR Reporting Responsibilities:**

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
  - a. Unexpected (in terms of nature, severity, or frequency) given
    - i. (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
    - ii. (b) the characteristics of the subject population being studied;
  - b. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
  - c. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of

physical or psychological harm than was previously known or recognized.

2. If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the OCR for each site's IRB of record along with the report of the adverse event.
3. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at OCR.
4. SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions is as directed by FDA guidelines (<http://www.fda.gov/medwatch/index.html>). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

Food and Drug Administration:

Telephone 1-800-FDA-1088

Fax 1-332-FDA-0178

<http://www.fda.gov/medwatch/report.htm>

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology

Bristol-Myers Squibb Company

Fax Number: 609-818-3804

Email: [Worldwide.safety@bms.com](mailto:Worldwide.safety@bms.com)

## 10.7. OCR Reporting Responsibilities to BMS:

### • Serious Adverse Events (SAEs)

All Serious Adverse Events (SAEs) that occur on or after the first day of study treatment to 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety.

SAEs, whether related or not related to study drug, must be reported to BMS within 24 hours of becoming aware of the event. SAEs must be recorded on FDA MedWatch form 3500a.

**SAE Email Address:** [Worldwide.Safety@BMS.com](mailto:Worldwide.Safety@BMS.com)

**SAE Facsimile Number:** 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours of becoming aware of the changes to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

- **Pregnancy**

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including 23 weeks after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The sponsor must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

### **10.8. Pregnancy**

All WOCBP should be instructed to contact their site Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the event of a confirmed pregnancy in a patient participating in the study, the site Investigator must immediately notify the Fox Chase Cancer Center Study Monitor who will notify Dr. Matthew Zibelman.

## **11.0 Measures of Effect**

Provide response criteria. If RECIST criteria below are not applicable delete the following text and provide disease appropriate criteria with references.

### **11.1. Response Evaluation Criteria in Solid Tumors (RECIST)**

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment. Assessments will be performed after every two cycles of treatments. Once protocol treatment has been completed subjects will be assessed every three months or sooner as indicated and judged by treating physicians.

### **11.2. Definitions**

Please use or modify the following text as appropriate.

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*Version Date 06/16/2019*

Evaluable for adverse events. All patients will be evaluable for adverse events from the time of their first treatment with Axitinib and Nivolumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

### **11.3. Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm by chest x-ray, as  $\geq 10$  mm with CT scan, or  $\geq 10$  mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.



Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

#### **11.4. Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

## **11.5. Response Criteria**

### **11.5.1. Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

### **11.5.2. Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Sponsor-Investigator).

### For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD /not evaluated	No	PR	
SD	Non-CR/Non-PD /not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>.” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

### For patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
<p>* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised</p>		

### 11.6. Objective response rate (ORR)

Objective response rate (ORR) is defined as the proportion of subjects with metastatic RCC who achieve a best response of complete response (CR) or partial response (PR) using the RECIST 1.1 criteria. It will be determined by the investigator for each subject as either CR or PR and will be calculated as percentage CR + PR.

### 11.7. Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

## 12.0 Statistical Considerations

The phase I portion of the study is based on a standard 3+3 dose escalation design enrolling 6-12 patients and will be used to determine DLTs and RP2D. The phase II portion of the study will enroll 43 patients each in two separate cohorts of patients – previously treated and treatment naïve – with advanced RCC with the primary goal of assessing the overall response rate in each cohort.

### Power and sample size:

Arm 1 (treatment naïve, first line): With 43 patients in this arm, we would be able to detect a 20% improvement in treatment response and achieve 82% power at the 5% significance level (one-sided). This calculation is based on a baseline response rate of 30% obtained from historical data. [5]

Arm 2 (prior TKI, no immunotherapy): With 43 patients in this arm, we would be able to detect a 19% improvement in treatment response and achieve 81% power at the 5% significance level (one-sided). This calculation is based on a baseline response rate of 19% obtained from historical data. [4]

### Early stopping rule for toxicity:

Evaluation of adverse events will be done separately in each cohort. We will stop the study early if 4 or more of the first 15 patients enrolled into each cohort experience a treatment related death or develop a grade 3 or grade 4 treatment related AEs that does not resolve or diminish in grade after 12 weeks of intervention. Intervention can include but is not limited to treatment discontinuation, administration of steroids, administration of immune modulatory agents, or other supportive measures. The table below lists the probability of early stopping due to adverse events based on pre-specified true probabilities of such events in these individuals.

Probability of stopping the study early due to adverse events in each cohort based on pre-specified true probabilities of such events

Probability of adverse event in an individual	10%	20%	30%	40%
Probability of stopping early due to adverse events	5.6%	35.2%	70.3%	90.9%

### 12.1. Analysis of Secondary Endpoints

Adverse events and laboratory abnormalities will be summarized by type, frequency and severity; and serum biomarkers will be summarized using descriptive statistics. Time-to-event endpoints such as duration of response, overall survival and progression-free survival will be analyzed and summarized using Kaplan-Meier methods.

### 12.2. Sample Size/Accrual Rate

We anticipate accrual of 92-98 total patients over 18 months.

### 12.3. Reporting and Exclusions

#### 12.3.1. Evaluation of toxicity:

All patients will be evaluable for toxicity from the time of their first treatment with axitinib and nivolumab.

#### 12.3.2. Evaluation of response:

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). An incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

## 13.0 Data and Safety Monitoring Plan

### 13.1. Monitoring Plan

FCCC OCR will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the OCR will collect and report data

to the study Sponsor Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the OCR and Sponsor Investigator as applicable.

### **13.2. Data Safety Monitoring Committee**

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed at least every 3 months by the Fox Chase Cancer Center Data Safety Monitoring Board (FCCC DSMB). In this capacity the FCCC DSMB will serve as an advisory committee to the Study Sponsor-Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee. The FCCC DSMB will review those aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Study Sponsor-Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Study Sponsor-Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

## **14.0 Administrative**

This study will be conducted in accordance with local, state and Federal regulations and according to accepted good clinical practice guidelines.

### **14.1. Data Reporting**

The FCCC Clinical Research Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit.

The OCR staff is responsible for compiling and submitting data to the Sponsor Investigator and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Data and Safety Monitoring Committee.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

The IST Regulatory Specialist is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, and study specific Serious Adverse Events.

### **14.2. Retention of Records**

Time points for the retention of records are described in detail in the contract between the grantor and the OCR and passed on to the participating site. Please refer to the

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study specific terms for specific time points. In all cases the FCCC Clinical Research Monitor must be notified of any plans to move records to an offsite location prior to doing so.

### **14.3. Study Agents**

Any study agent supplied through the OCR from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

### **14.4. Informed Consent**

The IRB approved informed consent documents must be signed by the patient before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

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9. Atkins, M.B., et al., *Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial*. *The Lancet Oncology*, 2018.



## 15.0 Appendix

### 15.1. Appendix I

#### Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE guidelines.

Treatment recommendations are provided below:

**For Grade 1 symptoms:** (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen), famotidine 20 mg PO or IV (or alternative H2 antagonist), and could consider addition of paracetamol at least 30 minutes before additional nivolumab administrations.

**For Grade 2 symptoms:** (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent), famotidine 20 mg IV or equivalent and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If patient continues to react, rate can be decreased sequentially by 50% as low as 1/8 rate and then increased as tolerated in cycle or with subsequent cycles. If patient is unable to tolerate at 1/8 rate or unable to be escalated, alternative options may need to be arranged with study team and medical monitor. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent), famotidine 20 mg IV or equivalent and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If

necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

**For Grade 3 or Grade 4 symptoms:** (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (eg. appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg. oral antihistamine, or corticosteroids).

## 15.2. Appendix II

### **Management for immune related Adverse Events**

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

#### **Pulmonary Adverse Events**

Pulmonary AEs have been observed following treatment with nivolumab. The frequency of pulmonary AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (eg. focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia.

#### **Pulmonary Adverse Event Management Algorithm**

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

<b>Grade of Pneumonitis</b>	<b>Management</b>	<b>Follow-up</b>
<b>Grade 1</b> Radiographic changes only	<ul style="list-style-type: none"> <li>• Consider delay of I-O therapy</li> <li>• Monitor for symptoms every 2-3 days</li> <li>• Consider Pulmonary and Infectious Disease (ID) consults</li> </ul>	<ul style="list-style-type: none"> <li>• Re-image at least every 3 weeks</li> </ul> <p><u>If worsens:</u></p> <ul style="list-style-type: none"> <li>• Treat as Grade 2 or 3-4</li> </ul>
<b>Grade 2</b> Mild to moderate new symptoms	<ul style="list-style-type: none"> <li>• Delay I-O therapy per protocol</li> <li>• Pulmonary and ID consults</li> <li>• Monitor symptoms daily, consider hospitalization</li> <li>• 1.0 mg/kg/day methylprednisolone IV or oral equivalent</li> <li>• Consider bronchoscopy, lung biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Re-image every 1-3 days</li> </ul> <p><u>If improves:</u></p> <ul style="list-style-type: none"> <li>• When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics</li> </ul> <p><u>If not improving after 2 weeks or worsening:</u></p> <ul style="list-style-type: none"> <li>• Treat as Grade 3-4</li> </ul>
<b>Grade 3-4</b> Severe new symptoms; New/worsening hypoxia; Life-threatening	<ul style="list-style-type: none"> <li>• Discontinue I-O therapy per protocol</li> <li>• Hospitalize</li> <li>• Pulmonary and ID consults</li> <li>• 2-4 mg/kg/day methylprednisolone IV or IV equivalent</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> <li>• Consider bronchoscopy, lung biopsy</li> </ul>	<p><u>If improves to baseline:</u></p> <ul style="list-style-type: none"> <li>• Taper steroids over at least 6 weeks</li> </ul> <p><u>If not improving after 48 hours or worsening:</u></p> <ul style="list-style-type: none"> <li>• Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)</li> </ul>

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

### **Gastrointestinal Adverse Events**

Gastrointestinal AEs have been observed following treatment with nivolumab. Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

### **GI Adverse Event Management Algorithm**

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

<b>Grade of Diarrhea/ Colitis</b>	<b>Management</b>	<b>Follow-up</b>
<b>Grade 1</b> <u>Diarrhea</u> : < 4 stools/day over baseline; <u>Colitis</u> : asymptomatic	<ul style="list-style-type: none"> <li>• Continue I-O therapy per protocol</li> <li>• Symptomatic treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Close monitoring for worsening symptoms.</li> <li>• Educate patient to report worsening immediately</li> </ul> <u>If worsens:</u> <ul style="list-style-type: none"> <li>• Treat as Grade (G) 2 or 3/4</li> </ul>
<b>Grade 2</b> <u>Diarrhea</u> : 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL <u>Colitis</u> : abdominal pain; blood in stool	<ul style="list-style-type: none"> <li>• Delay I-O therapy per protocol</li> <li>• Symptomatic treatment</li> </ul>	<u>If improves to grade 1:</u> <ul style="list-style-type: none"> <li>• Resume I-O therapy per protocol</li> </ul> <u>If persists &gt; 5-7 days or recur:</u> <ul style="list-style-type: none"> <li>• 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent</li> <li>• When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol.</li> </ul> <u>If worsens or persists &gt; 3-5 days with oral steroids:</u> <ul style="list-style-type: none"> <li>• Treat as grade 3/4</li> </ul>
<b>Grade 3-4</b>	<ul style="list-style-type: none"> <li>• Discontinue I-O therapy per protocol</li> </ul>	<u>If improves:</u>

<p><u>Diarrhea (G3):</u> <math>\geq 7</math> stools per day over baseline; incontinence; IV fluids <math>\geq 24</math> hrs; interfering with activities of daily living (ADL)</p> <p><u>Colitis (G3):</u> severe abdominal pain, medical intervention indicated, peritoneal signs</p> <p>G4: life-threatening, perforation</p>	<ul style="list-style-type: none"> <li>• 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> <li>• Consider lower endoscopy</li> </ul>	<ul style="list-style-type: none"> <li>• Continue steroids until grade 1, then taper over at least 1 month</li> </ul> <p><u>If persists &gt; 3-5 days, or recurs after improvement:</u></p> <ul style="list-style-type: none"> <li>• Add infliximab 5 mg/kg (if no contraindication).</li> </ul> <p>Note: Infliximab should not be used in cases of perforation or sepsis</p>
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Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

### **Hepatic Adverse Events**

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, DILI, have been observed following treatment with nivolumab and nivolumab in combination with ipilimumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved.

### **Hepatic Adverse Event Management Algorithm**

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

<b>Grade of Liver Test Elevation</b>	<b>Management</b>	<b>Follow-up</b>
<p><b>Grade 1</b></p> <p>AST or ALT <math>&gt; \text{ULN}</math> to <math>3.0 \times \text{ULN}</math> and/or Total bilirubin (T. bili) <math>&gt; \text{ULN}</math> - <math>1.5 \times \text{ULN}</math></p>	<ul style="list-style-type: none"> <li>• Continue I-O therapy per protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Continue liver function tests (LFT) monitoring per protocol</li> </ul> <p><u>If worsens:</u></p> <ul style="list-style-type: none"> <li>• Treat as Grade 2 or 3-4</li> </ul>
<p><b>Grade 2</b></p> <p>AST or ALT <math>&gt; 3.0</math> to <math>\leq 5 \times \text{ULN}</math> and/or T. bili <math>&gt; 1.5</math> to <math>\leq 3 \times \text{ULN}</math></p>	<ul style="list-style-type: none"> <li>• Delay I-O therapy per protocol</li> <li>• Increase frequency of monitoring to every 3 days</li> </ul>	<p><u>If returns to baseline:</u></p> <ul style="list-style-type: none"> <li>• Resume routine monitoring, resume I-O therapy per protocol</li> </ul> <p><u>If elevations persist &gt; 5-7 days or worsen:</u></p>

		<ul style="list-style-type: none"> <li>• 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol</li> </ul>
<b>Grade 3-4</b> AST or ALT > 5 x ULN and /or T.bili >3 x ULN	<ul style="list-style-type: none"> <li>• Discontinue I-O therapy*</li> <li>• Increase frequency of monitoring to every 1-2 days</li> <li>• 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent**</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> <li>• Consult gastroenterologist</li> </ul>	<u>If returns to grade 2:</u> <ul style="list-style-type: none"> <li>• Taper steroids over at least 1 month</li> </ul> <u>If does not improve in &gt;3-5 days, worsens or rebounds:</u> <ul style="list-style-type: none"> <li>• Add mycophenolate mofetil 1 gram (g) twice daily (BID)</li> <li>• If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines</li> </ul>

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

\*I-O therapy may be delayed rather than discontinued if AST/ALT  $\leq$  8 x ULN and T.bili  $\leq$  5 x ULN.

\*\*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

### **Skin Adverse Events**

Rash and pruritus were the most common skin AEs observed following treatment with nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

### **Skin Adverse Event Management Algorithm**

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Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Rash	Management	Follow-up
<b>Grade 1-2</b>  Covering $\leq$ 30% body surface area (BSA)	<ul style="list-style-type: none"> <li>• Symptomatic therapy (e.g. antihistamines, topical steroids)</li> <li>• Continue I-O therapy per protocol</li> </ul>	<u>If persists &gt; 1-2 weeks or recurs:</u> <ul style="list-style-type: none"> <li>• Consider skin biopsy</li> <li>• Delay I-O therapy per protocol</li> <li>• Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol</li> </ul> <u>If worsens:</u> <ul style="list-style-type: none"> <li>• Treat as Grade 3-4</li> </ul>
<b>Grade 3-4</b>  Covering >30% BSA; Life threatening consequences	<ul style="list-style-type: none"> <li>• Delay or discontinue I-O therapy per protocol</li> <li>• Consider skin biopsy</li> <li>• Dermatology consult</li> <li>• 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent</li> </ul>	<u>If improves to Grade 1:</u> <ul style="list-style-type: none"> <li>• Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections</li> <li>• Resume I-O therapy per protocol</li> </ul>

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

### **Renal Adverse Events**

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of RCC or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

### **Renal Adverse Event Management Algorithm**

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Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

<b>Grade of Creatinine Elevation</b>	<b>Management</b>	<b>Follow-up</b>
<b>Grade 1</b> Creatinine > upper limit of normal (ULN) and > than baseline but $\leq 1.5x$ baseline	<ul style="list-style-type: none"> <li>• Continue I-O therapy per protocol</li> <li>• Monitor creatinine weekly</li> </ul>	<u>If returns to baseline:</u> <ul style="list-style-type: none"> <li>• Resume routine creatinine monitoring per protocol</li> </ul> <u>If worsens:</u> <ul style="list-style-type: none"> <li>• Treat as Grade 2 or 3/4</li> </ul>
<b>Grade 2-3</b> Creatinine > 1.5x baseline to $\leq 6x$ ULN	<ul style="list-style-type: none"> <li>• Delay I-O therapy per protocol</li> <li>• Monitor creatinine every 2-3 days</li> <li>• 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent</li> <li>• Consider renal biopsy</li> </ul>	<u>If returns to Grade 1:</u> <ul style="list-style-type: none"> <li>• Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol</li> </ul> <u>If elevations persist &gt; 7 days or worsen:</u> <ul style="list-style-type: none"> <li>• Treat as Grade 4</li> </ul>
<b>Grade 4</b> Creatinine > 6x ULN	<ul style="list-style-type: none"> <li>• Discontinue I-O therapy per protocol</li> <li>• Monitor creatinine daily</li> <li>• 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent</li> <li>• Consult nephrologist</li> <li>• Consider renal biopsy</li> </ul>	<u>If returns to Grade 1:</u> Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

### **Neurologic Adverse Events**



Neurologic AEs have been uncommonly observed following treatment with nivolumab. Neurologic AEs can manifest as central abnormalities (eg, aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality).

### Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity	Management	Follow-up
<b>Grade 1</b> Asymptomatic or mild symptoms; Intervention not indicated	<ul style="list-style-type: none"> <li>Continue I-O therapy per protocol</li> </ul>	<u>Continue to monitor the patient.</u> <u>If worsens:</u> <ul style="list-style-type: none"> <li>Treat as Grade 2 or 3-4</li> </ul>
<b>Grade 2</b> Moderate symptoms; Limiting instrumental ADL	<ul style="list-style-type: none"> <li>Delay I-O therapy per protocol</li> <li>Treat symptoms per local guidelines</li> <li>Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent</li> </ul>	<u>If improves to baseline:</u> <ul style="list-style-type: none"> <li>Resume I-O therapy per protocol when improved to baseline</li> </ul> <u>If worsens:</u> <ul style="list-style-type: none"> <li>Treat as Grade 3-4</li> </ul>
<b>Grade 3-4</b> Severe symptoms; Limiting self-care ADL; Life-threatening	<ul style="list-style-type: none"> <li>Discontinue I-O therapy per protocol</li> <li>Obtain neurology consult</li> <li>Treat symptoms per local guidelines</li> <li>1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent</li> <li>Add prophylactic antibiotics for opportunistic infections</li> </ul>	<u>If improves to Grade 2:</u> <ul style="list-style-type: none"> <li>Taper steroids over at least 1 month</li> </ul> <u>If worsens or atypical presentation:</u> <ul style="list-style-type: none"> <li>Consider IVIG or other immunosuppressive therapies per local guidelines</li> </ul>

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

### Endocrinopathies

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Endocrinopathies have been observed following treatment with nivolumab. Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (eg, TSH) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

### Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

<b>Asymptomatic thyroid stimulating hormone (TSH) elevation</b>	<ul style="list-style-type: none"> <li>• Continue I-O therapy per protocol</li> <li>• If TSH &lt; 0.5 x lower limit of normal (LLN), or TSH &gt; 2 x ULN, or consistently out of range in 2 subsequent measurements: include free thyroxine (fT4) at subsequent cycles as clinically indicated; consider endocrinology consult</li> </ul>		
<b>Symptomatic endocrinopathy</b>	<table border="1"> <tr> <td data-bbox="646 1136 1040 1850"> <ul style="list-style-type: none"> <li>• Evaluate endocrine function</li> <li>• Consider pituitary scan</li> </ul> <p><u>Symptomatic with abnormal lab/pituitary scan:</u></p> <ul style="list-style-type: none"> <li>• Delay I-O therapy per protocol</li> <li>• 1-2 mg/kg/day methylprednisolone IV or by mouth (PO) equivalent</li> <li>• Initiate appropriate hormone therapy</li> </ul> <p><u>No abnormal lab/pituitary MRI scan but symptoms persist:</u></p> </td><td data-bbox="1040 1136 1382 1850"> <p><u>If improves (with or without hormone replacement):</u></p> <ul style="list-style-type: none"> <li>• Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections</li> <li>• Resume I-O therapy per protocol</li> <li>• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component</li> </ul> </td></tr> </table>	<ul style="list-style-type: none"> <li>• Evaluate endocrine function</li> <li>• Consider pituitary scan</li> </ul> <p><u>Symptomatic with abnormal lab/pituitary scan:</u></p> <ul style="list-style-type: none"> <li>• Delay I-O therapy per protocol</li> <li>• 1-2 mg/kg/day methylprednisolone IV or by mouth (PO) equivalent</li> <li>• Initiate appropriate hormone therapy</li> </ul> <p><u>No abnormal lab/pituitary MRI scan but symptoms persist:</u></p>	<p><u>If improves (with or without hormone replacement):</u></p> <ul style="list-style-type: none"> <li>• Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections</li> <li>• Resume I-O therapy per protocol</li> <li>• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component</li> </ul>
<ul style="list-style-type: none"> <li>• Evaluate endocrine function</li> <li>• Consider pituitary scan</li> </ul> <p><u>Symptomatic with abnormal lab/pituitary scan:</u></p> <ul style="list-style-type: none"> <li>• Delay I-O therapy per protocol</li> <li>• 1-2 mg/kg/day methylprednisolone IV or by mouth (PO) equivalent</li> <li>• Initiate appropriate hormone therapy</li> </ul> <p><u>No abnormal lab/pituitary MRI scan but symptoms persist:</u></p>	<p><u>If improves (with or without hormone replacement):</u></p> <ul style="list-style-type: none"> <li>• Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections</li> <li>• Resume I-O therapy per protocol</li> <li>• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component</li> </ul>		

	<ul style="list-style-type: none"> <li>• Repeat labs in 1-3 weeks /MRI in 1 month</li> </ul>	
<b>Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)</b>	<ul style="list-style-type: none"> <li>• Delay or discontinue I-O therapy per protocol</li> <li>• Rule out sepsis</li> <li>• Stress dose of IV steroids with mineralocorticoid activity</li> <li>• IV fluids</li> <li>• Consult endocrinologist</li> <li>• If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy</li> </ul>	

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

### 15.3. Appendix III

Dose escalation/de-escalation decision rules

<b>First 3 patients on Dose Level 0 (DL0)</b>	
0 out of 3 DLT	Escalate to DL+1 and accrue 3 patients.
1 out of 3 DLT	Keep at DL0 and accrue 3 more patients.
$\geq 2$ DLT	De-escalate to DL -1.
<b>For patients escalated to Dose Level +1 (DL+1)</b>	
0-1 out of 3 DLT	Keep at Dose Level +1 and accrue 3 more patients. If 0-1 DLT out of 6 patients at DL+1, this is RP2D.
$\geq 2$ DLT	De-escalate back to DL0 and accrue 3 patients. If 6 patients have already been treated at DL0 with 0-1 DLT, declare DL0 as RP2D.
<b>Once 6 patients accrue to DL0</b>	
0-1 DLT	DL0 is RP2D.
$\geq 2$ DLT	De-escalate to DL-1 and accrue 3 patients.
<b>For patients de-escalated to DL-1</b>	
0-1 out of first 3 patients	Keep at DL-1 and accrue 3 patients. If no more than 0-1 DLT out of 6 patients at DL-1, declare this as RP2D.
$\geq 2$ DLT	Stop study for toxicity.